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Review Article

Understanding the essentials of drug interactions: A potential need for safe and effective use of drugs

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Abstract
Drug interactions (DIs) represent an important and widely under recognized source of medication errors. An interaction is said to occur when the effects of one drug are changed by the presence of another drug(s), food, drink or an environmental chemical. When a therapeutic combination could lead to an unexpected change in the condition of the patient, this would be described as an interaction of potential clinical significance. DIs can arise in numerous ways; such as pharmacodynamic interaction, in which receptor effects of different agents interacts to produce synergy or antagonism of drug effects. In pharmacokinetic interaction, the blood levels of given agents may be raised or lowered based on the type of interaction. Special attention and thorough monitoring is needed for the patients who are predisposed to develop DIs and those on drugs with narrow therapeutic index. DIs can be a very important contributory factor for the occurrence of adverse drug reactions and adverse drug events. DIs monitoring programs should be initiated and strengthened in order to minimize their occurrence. Herbal drug interactions and DIs comprising over the counter medicines should also be considered seriously.

Key words: Drug interaction, Herbal drug interactions, Drug interaction monitoring, Over the counter medications

Drug interactions (DIs) represent an important and widely under recognized source of medication errors.[1] Literatures of drug-drug interactions (DDIs) in the 1960s were based primarily on animal experiments, with a few case reports. Clinical reports seemed to focus on oral anticoagulants or on interactions of the monoamine oxidase inhibitors only. With practitioners noting more drug interactions in 1970s and 1980s, publication of both case reports and clinical studies increased.[2] In this article, the authors provides an overview of DIs with special emphasises on drug-drug interactions (DDIs). The authors have also attempted provide an overview regarding the strategies to minimize the occurrence of DIs.

Definition of drug interactions: An interaction is said to occur when the effects of one drug is changed by the presence of another drug(s), food, drink or an environmental chemical.[3] When a therapeutic combination could lead to an unexpected change in the condition of the patient, this would be described as an interaction of potential clinical significance. The net effect of the combination may be synergism or additive effect of one or more drugs, antagonism or negative effect of one or more drugs, alteration of effect of one or more drugs or the production of idiosyncratic effects.[4]

Epidemiology of drug interactions: The incidence of adverse drug interactions has been estimated to be between 2.2 and 30% in hospitalized patients and between 9.2 and 70.3% in ambulatory patients.[5, 6, 7, 8] Drug interactions are important in clinical practice and have been estimated to account for 6-30% of all adverse drug reactions (ADRs).[9]

A review of nine studies of the epidemiology of DDIs in hospital admissions found that the reported incidence ranged from 0-2.8%.[10] In the Harvard Medical Practice Study of adverse events, 20% of events in an acute hospital in-patient setting were drug related. Of these, 8% were considered to be due to DDIs.[11] The Boston Collaborative Drug Surveillance Program examined 83,200 drug exposures in 9,900 hospitalized patients and identified 3,600 ADRs. A total of 234 (6.5%) adverse drug reactions caused were attributed to DIs.[12]

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Although the overall incidence of adverse drug interactions is probably quite low (<1%), it is still a considerable problem in terms of the global number of patients at risk and its potential for morbidity and mortality.[4] Each year a number of deaths occur as a direct result of patients taking a new prescription drug in combination with their existing medication regimen. A small number of drugs are withdrawn from market annually because patients experience harmful ADRs. [13] We could not locate the epidemiological data regarding DIs from Nepal.

Predisposing factors for drug interactions: There are various factors, contributing to the occurrence of DIs. This includes multiple pharmacological agents, multiple prescribers, use of non prescription drugs, drug abuse and patient noncompliance. Various patient variables are also implicated for drug interactions, i.e. age, genetic factors, disease states, renal function, hepatic function, alcohol consumption, smoking, diet, environmental factors, individual variations etc.[14]

Although in a limited number of cases, prescribers use known interactions to enhance efficacy in the treatment of several important conditions, patients are exposed to unnecessary risks by the concomitant prescription of agents that have been shown to interact adversely. Many interactions are predictable, i.e. they can be avoided, if the prescriber keeps himself updated with the clinical pharmacology of the medicines involved.[15]

Polypharmacy and interactions: Possibility of DIs is definitely higher in a country like Nepal where polypharmacy is common due to lack of strict regulation and monitoring. In a study conducted among medical outpatients in a teaching hospital, the mean ± SD number of drugs per prescription was 2.16±1.71 (range 0-10).[16] Also, a retrospective study on prescribing patterns for 100 randomly selected geriatric patients admitted over a period of 1 year to the medical wards of the Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal showed a high prevalence of polypharmacy. In another study, during a hospital stay, 73% patients received more than five, 54% received more than eight, and 24% received more than nine drugs concurrently.[17] Information and studies on possible interactions due to the large number of drugs prescribed are lacking in Nepal. It is important for the prescribers or physicians and their patients to be aware of drug induced hazards, preventive measures and management approaches. Polypharmacy can be an important contributing factor for the occurrence of DDIs. A hospital based study found an ADR rate of 7% in patients taking 6-10 drugs, which increased to 40% in those taking 16-20 drugs.[18]

Types of drug interactions: Broadly DIs it may be classified as drug-disease interaction, drug-herbal interactions, drug-drug interactions and the miscellaneous type.

I. Drug-disease interaction:[4] Disposses considerable threats in patients suffering from various disease conditions involving renal and hepatic impairment and other conditions. Conditions that place patients at high risk for drug interactions are aplastic anemia, asthma, cardiac arrhythmia, intensive care patients, diabetes, epilepsy, and hypothyroidism. It is therefore always important to assess such conditions and adjust the required doses of the drugs.

II. Drug-herb interactions: In the past, very few case reports related to herb-drug interactions were reported, and many of the reactions could only be explained theoretically. Recently, however, there have been several reported cases of possible herb-drug interactions.[19] Herbal products can produce ADRs likely due to lack of standardization of content of natural products, variations in the strength of the active ingredient, contamination by fungal organisms, and adulteration with other potentially harmful natural products. [20] Some of the clinically significant drug-herb interactions are listed in the Table 1 below:

Table 1: Drug- herbal interactions

S.No	Herbal drugs (Botanical name)	Outcomes
1.	Ginseng *(Panax ginseng)*	concurrent use of ginseng and antidiabetic agents may result in increased risk of hypoglycemia. [21]
2.	Garlic *(Allium sativum)*	concurrent use of garlic and anticoagulants may result in increased risk of bleeding. [22]
3.	St. Johns wort *(Hypericum Perforatum)*	concurrent use of digoxin and St John's wort may result in reduced digoxin efficacy. [23]
4.	Ginger *(Zingibar officinale)*	concurrent use of ginger and anticoagulants may result in increased risk of bleeding. [24]
5.	Gink biloba (*Ginkgo biloba)*	concurrent use of ginkgo and nonsteroidal antiinflammatory agents may result in an increased risk of bleeding. [25]

III. Drug-drug interactions: This includes both prescription and over-the counter (OTC) medicines. For example taking the antibiotic Ciprofloxacin with antacids lowers Ciprofloxacin's effectiveness. Similarly, there can be major drug interactions if Digoxin and Amiodarone are taken together. This combination can lead to increased Digoxin toxicity. In general, among the different types of DIs, the DDIs gain more importance because of their high incidence rate and the serious outcomes.

Mechanism behind DDIs: DDIs can arise in numerous ways. A wide array of pharmacodynamic interaction exists, in which effects of different agents on receptors interacts to produce synergy or antagonistic effects. In pharmacokinetic interaction, the blood levels of given agents may be raised or lowered. Two key systems that significantly influence drug levels have been found, namely the CYP450 and the P-glycoprotein transporters. [1,26]

Important interactions include the interactions which affects the CYP450 super family. These enzymes are responsible for the metabolism of the majority of pharmaceutical agents. Variations and alterations in CYP450 function have been implicated in minor and also in catastrophic adverse drug interactions to medications at therapeutic doses. CYP450 enzyme inhibition can be classified as either reversible or irreversible. The most common one is also called competitive inhibition. This inhibition is of transient type and the enzyme returns to normal activity once the inhibitor has been cleared. In irreversible inhibition, the enzyme structure is altered so that there is permanent enzyme inactivation. Enzyme activity can be restored only by synthesis of new enzymes. Similarly, enzyme induction refers to an increase in enzyme activity. Induction results from either increased production of enzyme (through enhanced transcription and translation) or through a reduction in the natural rate of enzyme breakdown.[26] Most clinically significant drug interactions are caused by Phase I hepatic microsomal enzymes rather than by Phase II metabolism. [27] In general, the lower the therapeutic index of a drug, the more serious the potential consequences of drug interactions affecting its metabolism.[13] Few examples listing the various mechanisms of drug interactions are given below in the table below.

Table 2: Types of interactions [4, 14, 28,]

Types on interactions	Mechanism	Examples
Pharmacokinetic interactions	inhibition of absorption	Ciprofloxacin chelates with cations e.g. aluminium, iron.
	inhibition of the enzyme CYP3A4	increased the risk of toxicity from Simvastatin, Carbamazepine etc
	enzyme inhibitors resulting in reduced drug effects:	inhibitors of CYP2D6 impair the therapeutic effect of codeine.
	enzyme induction resulting in reduced drug effects	induction of CYP3A4 can have profound effect on object drug.
	enzyme induction resulting in toxic metabolites	induction of enzyme leading to paracetamol toxicity.
	altered renal elimination	renal excretion of Digoxin is altered by Amiodarone, Quinidine
Pharmacodynamic interactions	additive pharmacodynamic effects	concomitant administration drugs that prolong the QTc interval resulting in ventricular arrhythmias.
	antagonistic pharmacodynamic effects	NSAIDs may inhibit the antihypertensive effect of drugs as ACE inhibitors.

Clinically significant drug interactions: Some of the clinically significant are listed below in Table 3.

Table 3: Clinically significant DDIs

Interacting drugs	Probable mechanism	Outcomes
Warfarin-aspirin	displacement of Warfarin from plasma albumin, inhibition of metabolism of Warfarin, direct hypoprothrombinemic effect of aspirin, gastric erosion	potential for serious gastrointestinal bleeding. [29]
Warfarin-Sulfamethoxazole(Component in Co-trimoxazole)	inhibition of Warfarin metabolism, displacement of Warfarin from protein binding sites	concurrent use of Warfarin and Sulfamethoxazole may result in an increased risk of bleeding. [30]
Warfarin-Macrolides	decreased Warfarin metabolism	there will be increase effect of Warfarin with potential for bleeding. [31]
Phenytoin-Carbamazepine	inhibition of Cytochrome P450 2C19-mediated metabolism of Phenytoin by Carbamazepine	concurrent use of Phenytoin and Carbamazepine may result in increased Phenytoin concentrations and decreased Carbamazepine concentrations. [32]
Phenytoin-Phenobarbitone	induction or inhibition of phenytoin metabolism	concurrent use of Phenytoin and Phenobarbital may result in increased or decreased Phenytoin levels. [33]
ACEIs-Potassium supplements	lowered aldosterone levels	elevated serum potassium level. Inhibition of ACE results in decreased aldosterone production and potentially decreased potassium excretion. [34]
ACEIs-Spironolactone	increased potassium retention secondary to lowered aldosterone levels	there may be elevated serum potassium level. [35]
Digoxin-Amiodarone	inhibition of p-glycoprotein by Amiodarone, and reduction of Digoxin clearance	may lead to Digoxin toxicity. [36]
Digoxin-Verapamil	inhibition of renal and/or extrarenal Digoxin clearance	can lead to Digoxin toxicity. [37]
Sulfonyl ureas-NSAIDs	displacement of Glibenclamide from plasma protein binding sites.	concurrent use of Glibenclamide and Aspirin may result in increased risk of hypoglycemia. [38]
Theophylline-Quinolones	decreased clearance of Theophylline	can lead to Theophylline toxicity. [39]
Warfarin-Omeprazole	decreased Warfarin metabolism	may result in elevation of International Normalized Ratio, serum values and potentiation of anticoagulant effects. [40]

Common drugs causing interactions: Anticoagulants, some antidiabetic drugs, particularly sulphonylureas, anticonvulsant drugs, tricylic antidepressants, antiarrhythmic drugs including Digoxin, NSAIDs including Aspirin, Neuroleptic drugs and Lithium, many anticancer and immunosuppressive agents and theophylline are some of the drugs that are commonly known to cause interactions. [15]

IV. Miscellaneous DIs: This includes interaction of drugs with dietary supplements, food and beverages, cigarette smoke etc.

Vitamin K is present in many vegetables. It promotes production of blood-clotting factors that may reduce the effectiveness of anticoagulants medicines like Warfarin. There have been also reports of reduction in the efficacy of Warfarin with intake of huge quantities of ice cream.[41]

Vitamin B6 (Pyridoxine) found in avocados, beans, peas, sweet potatoes, bacon, beef liver, pork, tuna, and some nonprescription vitamin-mineral products, increases the metabolism of Levodopa, producing decreased blood levels of Dopamine and parkinsonism effects. [42]

Concurrent use of Theophylline and tobacco may result in decreased theophylline concentrations. Theophylline doses may need to be reduced by 25% to 33% after discontinuation of tobacco smoking. Monitoring of theophylline plasma concentrations may be necessary to optimize therapy.[43]

Clinical management of DIs: Clinical management of drug-drug interactions should include prospective study on concurrent diseases and drugs being given to the patients. Follow-up monitoring of a patient's therapy and making appropriate adjustments in the drug regimen can circumvent potentially significant drug interactions. [15]

Recognizing DIs: DIs have an enormous impact on patient care and the pervasively poor recognition of DDIs is a part of the problem. In order to treat the patient safely and in a competent manner the concerned physicians should be aware of DDIs and should be able to detect them. DIs are more likely in elderly patients and in patients with renal and hepatic impairment. Any agent with low to medium therapeutic index can have its blood level dangerously increased through DDIs.[1] It should be noted that adverse drug interactions are predictable and therefore preventable. [15]

Strategies to prevent DDIs: Drug therapy becomes more complex as the diseases progress and because many patients are being treated with two or more drugs, the chances of DDIs increase. Hence, keeping complete and current medication records of the patients, closer monitoring and supervision of drug therapy is needed so as to prevent the problems and detect them at an early stage in their development. In order to reduce the occurrence of DDIs always identify the patient risk factors, take a through history, be knowledgeable about the drugs being used, consider therapeutic alternatives when possible and always educate the patients, monitor and individualize the therapy.[14]

For the prevention of the DDIs:

1. one should be able to detect and recognize the drug interaction related signs and symptoms.
2. It is always better to choose a drug with higher therapeutic index provided they are of comparable efficacy.
3. Therapeutic drug monitoring for the drugs with narrow therapeutic index is always advisable.
4. As the number of drugs per prescription increases so does the risk of drug interactions, It is always necessary to optimize the number of drugs per prescription. Even if in the situation, where the interacted drugs have to be given, proper monitoring of the relevant interaction outcomes and taking subsequent measures to minimize them, can decrease drug interaction related risks.

Obtaining information on DIs: Various sources of drug information can be referred so as to make the therapeutic decisions more patient oriented. Various sources of drug information are listed below in table 4. Since the data regarding DIs are huge and keeps on changing, there is a need for the availability of unbiased drug information.

Table 4: Sources of information on drug interactions

Sources	Comments
Martindale: the extra pharmacopoeia	provides information on drug interactions along with a monograph of individual drugs. It also gives information regarding the management of DIs.
American Society of Health System Pharmacists (AHFS)	gives the effect of drug interaction on the hepatic clearance and significant interacting combinations.
Micromedex Drug-Reax	it's a software which classifies drug interaction based on their onset, severity and documentation
British National Formulary (BNF)	lists the drug interactions of various drugs in its appendix
Nepal Drug Review (NDR)	has a section on drug interactions

Drug interaction with over the counter (OTC) medication: OTC medications are the ones that are dispensed from pharmacy without a prescription. Due to the hilly terrain in Nepal, the poor socioeconomic status, the high cost of modern medicines and non-availability of doctors in rural areas, difficulties arise in accessing modern healthcare. Drug retail shops frequently serve as the public's first point of contact with the healthcare system, leading to the practice of self-medication.[44] Self medication can attribute to the occurrence of DIs. Some of the common DIs that can occur with the OTC medications is listed in table 5.

Table 5: Drug interaction with OTC medications

OTC Drug	Interactions and outcomes
Acetaminophen	concurrent use of Acetaminophen and Phenytoin may result in decreased Acetaminophen effectiveness and an increased risk of hepatotoxicity. [45] concurrent use of Acetaminophen and Zidovudine may result in neutropenia; Acetaminophen toxicity (hepatotoxicity) [46] concurrent use of Isoniazid and Acetaminophen may result in an increased risk of hepatotoxicity. [47]
Aspirin	concurrent use of Aspirin and Ibuprofen may result in decreased antiplatelet effect of Aspirin.[48] concurrent use of Heparin and Aspirin may result in an increased risk of bleeding. [49] concurrent use of Aspirin and Enalapril may result in decreased effectiveness of Enalapril. [50]
Ibuprofen	concurrent use of Methotrexate and Ibuprofen may result in an increased risk of Methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations). [51] concurrent use of Phenytoin and Ibuprofen may result in an increased risk of Phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor), especially in renally impaired patients. [52]
Omeprazole	concurrent use of Digoxin and Omeprazole may result in an increased risk of Digoxin toxicity (nausea, vomiting, and arrhythmias). [53] concurrent use of Alprazolam and Omeprazole may result in benzodiazepine toxicity (CNS depression, ataxia, lethargy).[54] concurrent use of Ampicillin and Omeprazole may result in reduced Ampicillin bioavailability. [55]
Ranitidine	concurrent use of Ranitidine and Ketoconazole may result in decreased Ketoconazole effectiveness. [56] concurrent use of Ranitidine and Metformin may result in an increase in Metformin plasma concentrations. [57] concurrent use of Ranitidine and Theophylline may result in Theophylline toxicity (nausea, vomiting, palpitations, seizures). [58]

In general, before taking an OTC medication a patient should ask the following questions to the healthcare providers the following questions. [59]

1. Can I take it with other drugs?
2. Should I avoid certain foods, beverages or other products?
3. What are possible drug interaction signs I should know about?
4. How will the drug work in my body?
5. Is there more information available about the drug or my condition (on the Internet or in health and medical literature)?

In Nepal, even the non-OTC medications can be obtained without having a prescription and hence the risk of DI is very high.

Drug interaction monitoring program: Occurrence of drug interactions should be monitored closely in susceptible patients and in patients on drug combinations with likelihood of interactions. A team consisting of physician, pharmacologists, pharmacists and nurses should keep a close eye on the patient's conditions, medication and the prognosis. For the early detection and prevention of DIs there is a need for establishing DI monitoring programs. The DI monitoring program should identify the DIs occurring in the hospital, develop intervention strategies and evaluate the impact of the interaction.

The identification of the DIs can be done by maintaining the patient profile and checking the interactions based on the existing literature. The mentioned sources in table 4 may be beneficial for this purpose. The interactions should be categorized based on their severity. Following these steps, strategies should be made in order to prevent the occurrence of interactions, at least the severe ones. The intervention strategies may include peer group discussion, discussion among the Drug and Therapeutics Committee (DTC) members and discussion with junior doctors etc. Following the intervention the impact of the intervention should be analyzed by comparing the incidence with the pre intervention data. The importance of DIs should be taught to the medical students, pharmacists and nurses so that a team effort can be made by them in the future.

Conclusion

Drug interactions are often neglected and not considered seriously. DIs alone, can be a very important contributory factor for the occurrence of adverse drug reactions and adverse drug events. As polypharmacy is one of the cardinal causes for DDIs, a thorough review of the patient condition and medications should be carried out before prescribing or while adding new drugs to their existing drug regimen. If a particular DI is unavoidable, the patient experiencing the DI should be monitored for the safety and efficacy of the drug provided.

References

1. Sandson N. Drug-drug interaction: the silent epidemic. *Psychiatric Services* 2005; 56(1): 22-4.
2. Hartshorn EA. Evolution of drug-drug interactions: a personal viewpoint. Ann Pharmacother 2006; 40: 112-3.
3. Stockley I H. Drug interaction: a source book of adverse interaction, their mechanisms, clinical importance and management. 5th ed. Pharmaceutical Press, London 1999.
4. Lee A, Stockley IH. Drug interactions In Walker R, Edwards C. Clinical Pharmacy and Therapeutics. 3rd edition. Churchill Livingstone, Philadelphia 2003: 21-31.
5. Gosney M, Tallis R. Prescription of contraindicated and interacting drugs in elderly patients admitted to hospital. Lancet 1984; 1: 564-7
6. Kinney E. Expert system detection of drug interactions: results in consecutive patients. Comput Biomed Res 1986; 19: 462-7.
7. Dambro MR, Kallgren MA. Drug interaction in a clinic using COSTER. Comput Biol Med 1988; 18:31-8,
8. Shinn AF, Shrewsbury RP, Anderson KW. Development of a computerized drug database (MEDICOM) for use in a patient specific environment. Drug Inf J 1983; 17:205-10.
9. Classen DC, Pestotnick SL, Evans RS, Burke JP. Computer surveillance of adverse drug events in hospital patients. JAMA 1991; 266: 2847-51.
10. Jankel C A, Fitterman L K. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug safety 1993; 9 (1): 55-9.
11. Leape L, Brennam T A, Laired N et al. The nature of adverse events in hospitalized patients: results of the Harvard Medical Practice Study II. N Engl J Med 1992; 324: 377-84.
12. Boston Collaborative Drug Surveillance Program: Adverse drug interactions. JAMA 1972; 220: 1238-9
13. Brown CH. Overview of drug interactions. US Pharm 2000; 25: HS3- HS30.
14. Hussar DA. Drug interaction. In: Gennaro, Marderosian AHD, Hanson GR et al. Remington The science and practice pf pharmacy. Philadelphia: Lippincott Williams and Willinks; 2000: P: 1746-61.

15. Thomas A, Routledge PA. Drug interaction in clinical practice. Focus. Quarterly bulletin of pharmacovigilance. May 2003
16. Shankar PR, Partha P, Nagesh S. Prescribing patterns in medical outpatients. Int J Clin Pract 2002; 56: 549-1.
17. Joshi MP, Sugimoto T, Santoso B. Geriatric prescribing in the medical wards of a teaching hospital in Nepal. Pharmacoepidemiol Drug Saf 1997; 6: 417-21.
18. Smith J W, Seild L G, Cluff L E. Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. Ann Intern Med 1969; 65: 629.
19. Lambrecht JE, Hamilton W, Rabinovich A. A Review of Herb-Drug Interactions: Documented and Theoretical. US Pharmacist 2000; 25 (8):42-53.
20. Cupp MJ. Herbal Remedies: adverse effects and drug interactions. Am Fam Physician 1999; 59(5): 1239-45.
21. Vuksan V, Stavro SP, Sievenpiper JL et al. Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. Diabetes Care 2000; 23(9): 1221-26.
22. Legnani C, Frascaro M, Gauzzaloca G et al. Effects of a dried garlic preparation on fibrinolysis and platelet aggregation in healthy subjects. Arzneimittelforschung 1993; 43(2): 119-22.
23. Hennessy M, Kelleher D, Spiers JP et al. St. John's Wort increases expression of P-glycoprotein: implications for drug interactions. Br J Clin Pharmacol 2002; 53(1): 75-82.
24. Kruth P, Brosi E, Fux R et al. Ginger-associated overanticoagulation by phenprocoumon. Ann Pharmacother 2004; 38: 257-60.
25. Meisel C, Johne A, Roots I. Fatal intracerebral mass bleeding associated with Ginkgo biloba and ibuprofen. Atherosclerosis 2003; 167(2): 367.
26. Sikka R, Magauran B, Ulrich A, Shannon M. Bench to bedside: Pharmacogenomics, adverse drug interactions, and the Cytochrome P450 system. Acad Emerg Med 2005; 12(12): 1227-35.
27. Brosen K. Recent developments in hepatic drug oxidation: implications for clinical pharmacokinetics. Clin Pharmacokinet 1990;18: 220-39.
28. Beers MH, Berkow R. The Merck manual of diagnosis and therapy. 17th edition. New Jersy: Merck research laboratories; 1999.
29. Chan TYK. Adverse interactions between warfarin and nonsteroidal antiinflammatory drugs: mechanisms, clinical significance, and avoidance. Ann Pharmacother 1995; 29:1274-83.
30. Hassall C, Feetam CL, Leach RH et al. Potentiation of warfarin by co-trimoxazole (letter). Lancet 1975; 2: 1155.
31. Schwartz J, Bachmann K, Perrigo E. Interaction between warfarin and erythromycin. South Med J 1983; 76: 91-3.
32. Zielinski JJ, Haidukewych D. Dual effects of carbamazepine-phenytoin interaction. Ther Drug Monit 1987; 9: 21-3.
33. Hansten PD. Interactions between anticonvulsant drugs: primidone, diphenylhydantoin and phenobarbital. Northwest Med J 1974; 1: 17.
34. Chan TYK, Critchley JAJH. Life-threatening hyperkalaemia in an elderly patient receiving captopril, furosemide (frusemide) and potassium supplements. Drug Safety 1992; 7: 159-61.
35. Anon. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study (RALES)). Am J Cardiol 1996; 78: 902-7.
36. Product Information: Lanoxicaps(R), digoxin. GlaxoSmithKline, Research Triangle Park, NC, 10/2003.
37. Pedersen KE, Thayssen P, Klitgaard NA et al. Influence of verapamil on the inotropism and pharmacokinetics of digoxin. Eur J Clin Pharmacol 1983; 25: 199-206.
38. Kuback R, Antal E, Juhl R et al. Effects of aspirin and ibuprofen on the pharmacokinetics and pharmacodynamics of glyburide in healthy subjects. Ann Pharmacother 1996; 30: 20-6.
39. Wijnands WJA, Vree TB, Baars AM et al. Steady state kinetics of the quinolone derivatives ofloxacin, enoxacin, ciprofloxacin, and perfloxacin during maintenance treatment with theophylline. Drugs 1987; 34 (suppl 1): 159-69.
40. Sutfin T, Balmer K, Bostrom H et al. Stereoselective interaction of omeprazole with warfarin in healthy men. Ther Drug Monit 1989; 11: 176-84.
41. Mason P. Food and medicines. Pharmaceutical Journal 2002; 269:571-3.
42. Leon AS, Spiegel HE, Thomas G et al. Pyridoxine antagonism of levodopa in parkinsonism. JAMA 1971; 218: 1924 -7.
43. Jusko WJ. Influence of cigarette smoking on drug metabolism in man. Drug Metab Rev 1979; 9: 221-36.
44. Kafle KK, Madden JM, Shrestha AD et al. Can licensed drug sellers contribute to safe motherhood? A survey of the treatment of

pregnancy related anemia in Nepal. Soc Sci Med 1996; 42: 1577-88.
45. Brackett CC, Bloch JD. Phenytoin as a possible cause of acetaminophen hepatotoxicity: case report and review of the literature. Pharmacotherapy 2000; 20: 229-33.
46. Richman DD, Fischl MA, Grieco MH et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: a double-blind, placebo-controlled trial. N Engl J Med 1987; 317: 192-7.
47. Epstein MM, Nelson SD, Slattery JT et al. Inhibition of the metabolism of paracetamol by isoniazid. Br J Clin Pharmacol 1991; 31: 139-42.
48. Catella-Lawson F, Reilly MP, Kapoor SC et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. New Engl J Med 2001; 345(25): 1809-17.
49. Yett HS, Skillman JJ, Salzman EW. The hazards of aspirin plus heparin (letter). N Engl J Med 1978; 298: 1092.
50. Guazzi MD, Campodonico J, Celeste F et al. Antihypertensive efficacy of angiotensin converting enzyme inhibition and aspirin combination. Clin Pharmacol Ther 1998; 63:79-86.
51. Cassano WF. Serious methotrexate toxicity caused by interaction with ibuprofen (letter). Am J Pediatr Hematol Oncol 1989; 11: 481-2.
52. Jarosinski PF, Moscow JA, Alexander MS et al. Altered phenytoin clearance during intensive chemotherapy for acute lymphoblastic leukemia. J Pediatr 1988; 112: 996-9.
53. Oosterhuis B, Jonkman JH, Andersson T et al. Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. Br J Clin Pharmacol 1991; 32: 569-72.
54. Product Information: Prilosec(R), omeprazole. Astra Merck Inc., Wayne, PA, 1997.
55. Product Information: Prilosec(R), omeprazole. Astra Merck Inc., Wayne, PA, 1995.
56. Lelawongs P, Barone JA, Colaizzi JL et al. Effect of food and gastric acidity on absorption of orally administered ketoconazole. Clin Pharm 1988; 7:228-35.
57. Product Information: Avandamet(TM), rosiglitazone maleate and metformin hydrochloride. GlaxoSmithKline, Research Triangle Park, NC, 11/2003.
58. Fernandes E, Melewicz FM. Ranitidine and theophylline (letter). Ann Intern Med 1984; 100: 459.
59. USFDA. Drug Interactions: What You Should Know. Available on http://www.fda.gov/cder/consumerinfo/druginteractions.htm (Accessed last on 27th March 2006).